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Aluminum-containing vaccine associated adverse events: role of route of administration and gender

Phillip R. Pittman*

Division of Medicine, The United States Army Medical Research Institute of Infectious Diseases (USAMRIID), 1425 Porter Street, Fort Detrick, MD 21702-5011, USA

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Abstract

Anthrax vaccine, adsorbed (AVA) is a vaccine containing aluminum hydroxide that is administered as six subcutaneous (SQ) doses over 18 months. It is the only aluminum hydroxide licensed for SQ administration. To optimize the vaccination schedule and route of administration, a prospective pilot study comparing the use of fewer doses administered intramuscularly (IM) as well as SQ with the licensed schedule and route was performed. Data from that study on injection site reactions were extracted for this report. Erythema and induration occurred more commonly when the vaccine was administered SQ compared to IM ($P < 0.0001$, $P = 0.002$, respectively). SQ nodules were found only among the SQ group ($P < 0.0001$). Erythema, induration and SQ nodules were more common in women compared with men ($P < 0.001$) after the first SQ dose of AVA dose. Reaction rates decreased when the interval between the first two doses of AVA was increased from 2 to 4 weeks. © 2002 Published by Elsevier Science Ltd.

Keywords: Anthrax vaccine, adsorbed; *Bacillus anthracis*; Subcutaneous nodule; Gender differences

1. Introduction

Considerable interest in the role of aluminum hydroxide in vaccines has been generated by the apparent association of macrophagic myofascitis (MMF) among recipients of vaccines containing this compound in France [1]. All US-licensed vaccines containing aluminum hydroxide are administered intramuscularly (IM) except the anthrax vaccine, adsorbed (AVA), which is administered subcutaneously. AVA, an effective countermeasure against anthrax, was licensed for use in US in 1970 [2]. The product label recommends 0.5 ml SQ injections at 0, 2, and 4 weeks and 6, 12, and 18 months with annual revaccination as long as the individual is at risk of infection with anthrax [3]. In a serological analysis, it was shown that as the intervals between the first two doses of AVA increased from 2 to 4 weeks, the magnitude and rate of antibody response also increased [4]. The general safety of AVA when administered by the licensed route and schedule has been described in recent publications [2,5].

This report analyzes short-term injection site reactions when AVA is administered six subcutaneous (SQ) and IM. Gender differences are revealed. Although the primary objective of this randomized, open-label study was to select a two dose initial vaccination schedule and route of administration based on antibody response and reactogenicity, data were extracted for this report.

2. Methods

The protocol for this prospective, randomized, open-label study was approved by the institutional review boards at USAMRIID and the Office of the Surgeon General of the Army and submitted to the US Food and Drug Administration. Personnel conducting antibody assays were blinded to subjects, treatments and weeks of blood draw. All subjects gave written informed consent. This clinical research was conducted in accordance with ethical principles that have their origins in the Declaration of Helsinki and in accordance with federal regulations and guidelines.

2.1. Study subjects

Total enrollment for this study was 173 subjects. Subjects were not enrolled in the study if they were pregnant, HIV positive, or acutely ill with an oral temperature $\geq 38.3\,^{\circ}C$. Subjects were randomly assigned to receive AVA (0.5 ml per dose) according to 1 of 7 regimens. Six groups received the anthrax vaccine SQ or IM at week 0, weeks 0 and 2, or

* Tel.: +1-301-619-2997; fax: +1-301-619-2312.
E-mail address: phillip.pittman@det.amedd.army.mil (P.R. Pittman).

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weeks 0 and 4. The control group received SQ doses at 0, 2, and 4 weeks and 6, 12, and 18 months (licensed schedule).

2.2. Test article

AVA, a licensed product in United States, is prepared from a sterile culture filtrate containing the protective antigen of an avirulent strain of *Bacillus anthracis*, V770-NP1-R, which was adsorbed onto an aluminum hydroxide adjuvant. The vaccine was provided by BioPort Corporation (Lansing, MI) [3].

2.3. Safety evaluation

Volunteers were evaluated clinically at 30 min, 1–3 days, 1 week, and 1 month after each vaccination. Reactions were determined to be present or absent and graded for severity if present. Local reactions were measured for maximum dimension.

2.4. Statistical analysis

Systemic and local reaction rates were compared using Fisher exact tests and logistic regression analysis [6]. An intent-to-treat analysis was performed using all available data from all enrolled subjects.

3. Results

Mean age among the groups ranged from 32 to 35. Thirty-seven percent of the volunteers (64/173) were females. Fifty-eight percent (101/173) of the volunteers received the vaccine SQ. Of those, 21% (36/101) were females. No statistical difference was observed among the study groups for gender ($P = 0.678$) or age ($P = 0.965$).

3.1. Systemic reactions

Systemic vaccine-related adverse events recorded after each dose of AVA were independent of route, gender, or dose interval. No serious reaction that could be attributed to administration of the vaccine was observed. Headache, malaise, anorexia, and nausea were the most frequent complaints.

3.2. Local reactions

Comparing routes of administration, the most common local adverse event in doses 1–3 was tenderness at the injection site, IM 56%, SQ 70% ($P = 0.01$) (Table 1). The frequency of erythema, induration, warmth and SQ nodules were statistically more common in the SQ group compared to the IM group ($P < 0.0001$–0.005). There were no SQ nodules associated with IM administration of AVA.

Because of the increased frequency of local reactions associated with the SQ route of administration of AVA, volunteer demographics were evaluated for association with reactions. Race and age were not associated with reactions in this study. Table 2 shows the frequency of SQ nodules, erythema and induration by gender among volunteers administered AVA SQ. Local adverse events such as SQ nodules, erythema and induration were more common in women and associated with the SQ route of administration ($P < 0.0001$).

Table 3 shows the relationship between local reactions and timing between the first and second dose of AVA by route

Table 1
Selected injection site adverse events after initial doses of AVA intramuscular or subcutaneous

Adverse event (AE)	Intramuscular, $N = 118$, AE present[a], n (%)	Subcutaneous, $N = 203$, AE present[a], n (%)	P-value
Tenderness	66 (56)	143 (70)	0.01
SQ nodule	0	77 (38)	<0.0001
Erythema	7 (6)	74 (36)	<0.0001
Induration	2 (2)	31 (15)	0.002
Warmth	6 (5)	33 (16)	0.005

[a] AE: adverse event.

Table 2
AVA, selected adverse events by route and gender, after initial doses

Adverse event	Subcutaneous route		P-value
	Male, $N = 132$, AE present[a], n (%)	Female, $N = 71$, AE present[a], n (%)	
Subcutaneous nodule	32 (24.2)	45 (63.4)	<0.0001
Erythema	29 (22.0)	45 (63.4)	<0.0001
Induration	4 (3.0)	27 (38.0)	<0.0001

[a] AE: adverse event.

Table 3
Incidence of local adverse events after AVA dose 2 for women[a]

Reaction	Incidence (%)	P-value[b] vs. 0–2 SQ	P-value[b] 0–4 IM vs. 0–4 SQ
SQ nodule			
0–2 SQ	15/18 (83)		
0–4 SQ	4/10 (40)	0.035	0.087
0–2 IM	0/8 (0)	<0.001	
0–4 IM	0/10 (0)	<0.001	
Erythema			
0–2 SQ	13/18 (72)		
0–4 SQ	6/10 (60)	0.677	0.057
0–2 IM	0/8 (0)	<0.001	
0–4 IM	1/10 (10)	0.004	
Induration			
0–2 SQ	10/18 (56)		
0–4 SQ	1/10 (10)	0.041	1.000
0–2 IM	0/8 (0)	0.010	
0–4 IM	0/10 (0)	0.004	

[a] An analysis of similar data for men revealed no significant difference except for incidence of SQ nodules, 0–2 SQ versus 0–2 IM ($P = 0.023$).
[b] P-values by Fisher exact test ($P < 0.05$).

of administration for women. An increased interval between SQ doses from 2 to 4 weeks significantly decreased the rates of SQ nodules ($P = 0.035$), and induration ($P = 0.041$) in women after dose 2, but not edema (which increased) or erythema. In this small study, differences in the incidence of local reactions between SQ and IM routes were not detected with the 0–4 week schedule (SQ nodule, $P = 0.087$; erythema, $P = 0.057$; induration, $P = 1.0$) although the IM groups had lower reaction rates than the SQ groups. The only significant difference observed in men was a reduction in SQ nodules in the IM versus SQ groups given AVA at 0 and 2 weeks ($P = 0.023$).

Severity of local reaction, as determined by the dimensions of erythema and/or induration after injection, varied by both gender and route of AVA administration. Erythema and/or induration up to 50 mm occurred in 2.2% (1/46) of females and 4.2% (3/72) of males in the IM group ($P = 0.5664$). Whereas, 32% (23/71) of females and 15% (20/132) of males in the SQ group developed erythema and/or induration up to 50 mm. Volunteers in the IM group did not develop erythema and/or induration lesions greater than 50 mm. Twenty-five percent (18/71) of females and 7% (9/132) of males who were administered the vaccine SQ developed lesions 50–120 mm. Erythema and/or induration greater than 120 mm occurred in 4.2% (3/71) of females but not in males ($P < 0.0001$).

4. Discussion

Those preliminary data show that local reactions were statistically higher in women compared to men when AVA was administered SQ. After the first dose, the incidence of local reactions among males given AVA SQ versus IM were not statistically significant. The incidences of erythema, induration, and SQ nodules were significantly higher in women given AVA by the SQ route compared with the IM route. Local reactions decreased significantly in women when the AVA dose interval was increased from 2 to 4 weeks. The vast majority of these local reactions were not clinically significant (i.e. did not require medical attention or result in lost duty time). All reactions resolved completely without residua. Further details of the safety and immunogenicity of IM versus SQ routes of administration of AVA are presented in the article on the final reporting of this study [7].

Diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (ACEL-IMUNE) (DTaP), an aluminum adjuvant vaccine, has an erythema incidence of 35% ($N = 357$) and an induration incidence of 30% for dose 4 in infants and children (not stratified by gender). The rates are comparable to the SQ local reaction rates for AVA and are higher than the IM rates observed in this study [8].

This study focused on short-term adverse events. Whether MMF exists as a consequence of AVA administration will require long-term study. As its name implies, it has only been associated with IM administration of aluminum containing vaccines. It may be desirable to have sorted through the purported association of IM administration of aluminum-containing vaccines and MMF before changing route from SQ to IM, to have data showing the absence of the association in this country, or to have confirmatory data showing the occurrence of other adverse events in favor of such a route change.

AVA is the only vaccine containing aluminum hydroxide that is licensed for SQ administration. Our pilot study, though limited in scope, provides compelling evidence that the IM route of vaccine administration is associated with fewer short-term local adverse events than the SQ route. The reason for the gender difference in the rate of injection site reactions when AVA is administered SQ is not known. Similarly, the reason for the decrease in the rate of injection site reactions when AVA is administered 4 weeks rather than 2 weeks apart SQ is not known. A larger, randomized, placebo-controlled, double-blinded, multi-center study is planned to confirm and expand these findings.

References

[1] Gherardi RK, Coquet M, Cherin P, Authier FJ, Laforet P, Belec L, et al. Macrophagic myofascitis: an emerging entity. Groupe d'Etudes et Recherche sur les Maladies Musculaires Acquises et Dysimmunitaires (GERMMAD) de l'Association Francaise contre les Myopathies (AFM). Lancet 1998;352:347–52.

[2] Friedlander AM, Pittman PR, Parker GW. Anthrax vaccine: evidence for safety and efficacy against inhalational anthrax. JAMA 1999;282:2104–6.

[3] Anthrax vaccine adsorbed (package insert). Lansing: Michigan. Department of Public Health, 1978.

[4] Pittman PR, Mangiafico JA, Rossi CA, Cannon TL, Gibbs PH, Parker GW, et al. Anthrax vaccine: increasing intervals between the first two doses enhances antibody response in humans. Vaccine 2000;19:213–6.

[5] Centers for Disease Control & Prevention. Surveillance for adverse events associated with anthrax vaccination—US Department of Defense, 1998–2000. MMWR: Morb Mortal Wkly Rep 2000;49:341–5 [reprinted in JAMA 2000;283:2648–9].

[6] SAS Institute. SAS/STAT User's Guide, 6th ed., vol. 2. Cary (NC): SAS Institute, 1990.

[7] Pittman PR, Kim-Ahn G, Pifat DY, Coonan K, Gibbs P, Little S. et al. Anthrax vaccine: safety and immunogenicity of a dose-reduction, route comparison study in humans. Vaccine 2002;20:1412–20.

[8] Morgan CM, Blumberg DA, Cherry JD, Reisinger KS, Blatter MM, Blumer JL, et al. Comparison of acellular and whole-cell pertussis-component DTP vaccines. A multicenter double-blind study in 4–6-year-old children. Am J Dis Child 1990;144:41–5.